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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,530	12/18/2001	Pierre Legrain	EGYPSA 3.0-001	5557

530 7590 10/22/2003

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	12

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/023,530	LEGRAIN ET AL.	
	Examin r	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1,3-5,7,8,10,12,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,6,9,11 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 18 December 2001, which claims benefit of the U.S. Provisional application 60/256,276 filed 18 December 2000. The preliminary amendment filed 22 April 2002 has been entered.

Election/Restrictions

Applicant's election without traverse of Group II (claims 2, 6, 9, 11 and 13) in Paper No. 10 is acknowledged.

Claims 1, 3-5, 7, 8, 10, 12, 14 and 15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 2, 6, 9, 11 and 13 are presently under consideration.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (e.g., paragraphs 0054, 0092 and 0235). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Claim 9 is directed to a fragment of a polynucleotide comprising SEQ ID NO: 1 and 3. Because a nucleic acid comprising SEQ ID NO: 1 and 3 also comprises infinite undefined sequence, a claim to a fragment of that sequence would encompass infinite undefined sequence fragments. Amending the claim to read, for example, a nucleic acid comprising a fragment of the sequence set forth as SEQ ID NO: 1 and 3 would overcome this rejection.

Claim 10 is directed to a variant of a polynucleotide comprising SEQ ID NO: 1 and 3. The specification defines "variants" in paragraphs 0072-0074 as, "encoding a polypeptide variant of a given reference polypeptide" wherein the polypeptide generally maintains their functional characteristics. The specification states, "a variant of a polynucleotide may be a naturally occurring allelic variant or it may be a variant that is known naturally not to occur". Thus, the claim encompasses any polynucleotide encoding a polypeptide which generally maintains the

function of the polypeptides encoded by SEQ ID NO: 1 and 3. Further, the claims encompass naturally occurring allelic variants of the nucleic acids set forth as SEQ ID NO: 1 and 3.

First, it is noted that the claim does not limit the degree of structural variation in the polynucleotide or polypeptide encoded thereby or define "function" to mean a disclosed or known function of the polypeptide. Thus, the claims encompass any nucleic acid encoding a polypeptide having any function in common with the polypeptides encoded by SEQ ID NO: 1 or 3. Clearly there is no descriptive support for such a structurally and functionally divergent genus of polynucleotides. With regard to function, the specification discloses that the polypeptides encoded by SEQ ID NO: 1 and 3 interact with one another, and identify domains within TrCP (encoded by SEQ ID NO: 1) that interact with the polypeptide encoded by SEQ ID NO: 3. Thus, the specification provides descriptive support only for variants of SEQ ID NO: 1 limited to encoding a polypeptide having the function of interacting with the polypeptide encoded by SEQ ID NO: 3 and limited to comprising the domains shown to be required for the interaction. It does not appear that the required interacting domains within the polypeptide encoded by SEQ ID NO: 3 are disclosed in the application. Therefore, the specification does not adequately describe any polypeptides having the function of the polypeptide encoded by SEQ ID NO: 3 beyond the polypeptide explicitly disclosed (i.e., SEQ ID NO: 4). Therefore, only those variants of SEQ ID NO: 3 that encode SEQ ID NO: 4 meet the written description requirement of 35 U.S.C. §112, first paragraph.

With respect to naturally occurring allelic variants, the specification discloses only one allele within the scope of the genus for each of the claimed nucleic acids (i.e., SEQ ID NO: 1 or SEQ ID NO: 3). Beyond this detailed description of a single allele, there is no description of the

mutational sites that exist in nature and there is no description of how the structure of SEQ ID NO: 1 or 3 relates to the structure of any strictly neutral alleles. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. Therefore, the common attributes of the genus are not described and one of skill in the art would conclude that Applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is in sufficient to support the claim.

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claim is directed to a pharmaceutical composition comprising a recombinant host cell comprising a vector comprising SEQ ID NO: 1 or 3. Although the specification does not explicitly state that the claimed pharmaceutical composition is to be used for gene therapy, the only utility asserted in the specification for a pharmaceutical composition comprising a genetically modified host cell is *ex vivo* gene therapy (see paragraph 0163). Thus, it appears that the claims are directed to a product that is useful for *ex vivo* gene therapy.

State of the prior art and level of predictability in the art: At the time of filing, the art generally acknowledged that many difficulties remained to be overcome before findings obtained at the laboratory bench could be routinely translated into a successful gene therapy. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, " ... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that, "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene

therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Thus, the art clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

In an article published well after the effective filing date of the instant application, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remain unsolved even after the application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be**

overcome in the future", beginning on page 116 and continued through page 125). Thus, the art generally teaches that there remains much work to do before any *ex vivo* gene therapy approach is fully enabled.

With regard to the particulars of the instant claimed pharmaceutical composition, the art provides no therapeutic application for a recombinant host cell comprising a vector comprising SEQ ID NO: 1 or 3. The art teaches that β-TrCP (encoded by SEQ ID NO: 1) is an E3 ubiquitin ligase component that is involved in the ubiquitination and degradation of proteins such as IκBα and β-catenin (see, e.g., Laney *et al.* (1999) *Cell* 97:427-430; especially the discussion beginning in the paragraph bridging columns 1 and 2 on page 428). The art also teaches that overproduction of RASSF1 (encoded by SEQ ID NO: 3) can reduce the malignancy of a tumor cell line (see, e.g., Dammann *et al.* (2000) *Nat. Genet.* 25:315-319; especially the paragraph bridging pages 317-318). However, the teachings found in the art do not suggest any diseases that might be amenable to a treatment comprising administering a recombinant host cell comprising either one or both of SEQ ID NO: 1 and 2). Therefore, the skilled artisan is fully dependent upon the teachings of the specification: first, to teach what diseases will be treated using the claimed pharmaceutical composition and how to apply the claimed invention to treating those diseases; and, second, to overcome the hurdles that have generally hindered the translation of findings at the laboratory bench to effective gene therapies.

Amount of direction provided by the inventor and existence of working examples: The teachings in the specification provide that β-TrCP interacts with RASSF1 as evidenced by yeast two-hybrid analysis (see especially Example 6, beginning on page 37) and coimmunoprecipitation (see especially Example 8, beginning on page 40). The specification also provides that

inhibition of RasSF1 expression by RNAi results in decreased β-catenin expression, while overexpression of RasSF1C results in an increase in β-catenin expression (see especially Example 12, beginning on page 47). The specification concludes, "[the] interaction of RasSF1 with βTrCP could influence the activity of RasSF1 and its tumor suppressive functions in lung, breast and ovarian tumors. In particular the precise mapping of the interaction domains on both proteins could be used to modulate the function of RasSF1 in tumorigenesis in breast, lung, and ovarian tumors in which inactivation of RasSF1 has been associated with the cancer process" (page 48). However, none of these teachings suggest a condition that might be amenable to treatment using a pharmaceutical composition comprising a recombinant host cell comprising vectors comprising the nucleic acids set forth as SEQ ID NO: 1 or 3. The teachings in the art and specification suggest that the cell of the pharmaceutical composition might have a less malignant phenotype than an unmodified cancer cell; however, the skilled artisan would have no idea how to apply such a cell as a pharmaceutical.

With regard to overcoming the problems generally faced in translation of *in vitro* findings into a successful gene therapy protocol, the specification provides only a general overview of potential gene therapy vectors known in the art. There are no teachings in the specification directed to solving the problems encountered in developing gene therapies and nothing to suggest that, even if a suitable condition for treatment had been identified in the specification, the instant claimed pharmaceutical composition could be used successfully in light of the high degree of unpredictability in the gene therapy art.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not

be able to use the instant claimed invention without first engaging in undue experimentation. The teachings of the art and specification merely provide some limited molecular and cellular analysis of the polypeptides encoded by SEQ ID NO: 1 and 3, which provides no suggestion of what the skilled artisan should do with a pharmaceutical composition comprising a recombinant host cell comprising a vector comprising SEQ ID NO: 1 or 3. Thus, in order to use the claimed invention the skilled artisan would have to identify a condition that might respond to treatment with the claimed composition, develop technologies that would provide a suitable level and duration of expression of the recombinant nucleic acids, and identify an effective dose and route of administration. As the art and specification provide no guidance that would assist the skilled artisan in accomplishing any of these steps, the skilled artisan would clearly have to engage in undue trial and error experimentation to use the claimed composition.

Thus, due to the art recognized unpredictability of *ex vivo* gene therapy and the lack of guidance in the specification or prior art with regard to how to use the claimed pharmaceutical composition, it would require undue experimentation to practice the invention commensurate with the full scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 9-11 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is first indefinite in being directed to a "complex of polynucleotides". The teachings of the specification viewed as a whole do not indicate that the polynucleotides set forth as SEQ ID NO: 1 and 3 form a complex or interact directly in any way. Instead, it is the proteins encoded by the polynucleotides that form a complex. This aspect of the invention might be better conveyed by limiting the claim to a composition comprising isolated nucleic acids wherein nucleic acids comprising SEQ ID NO: 1 and SEQ ID NO: 3 are both present in the composition.

Claim 2 is also indefinite in the recitation of "the polypeptides". There is no antecedent basis for "the polypeptides" in the claim, which is independent of claim 1.

Claim 9 is indefinite in being directed to a fragment of a polynucleotide comprising SEQ ID NO: 1 and 3. It is unclear whether the fragment must comprise both SEQ ID NO: 3 or if the claim is directed to a fragment of either one of SEQ ID NO: 1 or 3. In the interest of compact prosecution the claim has been examined as directed to a fragment of SEQ ID NO: 1 or 3, according to its broadest reasonable interpretation. Likewise, claim 10 is indefinite in being directed a variant of a polynucleotide comprising SEQ ID NO: 1 and 3. The claim reads as though directed to a variant of a polynucleotide wherein both SEQ ID NO: 1 and SEQ ID NO: 3 are comprised within the same nucleic acid. It is unclear from the remainder of the disclosure whether Applicant intends for the nucleic acid to be limited to comprising both SEQ ID NO: 1 and 3. Again, the claim has been examined according to its broadest reasonable interpretation as encompassing a variant of a polynucleotide comprising either of SEQ ID NO: 1 or 3. If it is Applicant's intention that the claim be limited to a single nucleic acid comprising both SEQ ID NO: 1 and 3, this should be made clear in the response to this Office Action.

Claim 10 is additionally indefinite in the recitation of "said polynucleotide"; there is no antecedent basis for the limitation in the claim.

Claims 11 and 13 are indefinite in being drawn to a host cell comprising the "vectors" according to claim 6. It is unclear whether the use of the plural "vectors" instead of the singular indicates that the host cell must contain both of the vectors set forth in claim 6 (i.e., one comprising SEQ ID NO: 1 and one comprising SEQ ID NO: 3) or whether the host cell can comprise either one of the vectors. Again, the claim has been examined according to the broader scope (i.e., comprising either SEQ ID NO: 1 or SEQ ID NO: 3.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6, 9-11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Cenciarelli *et al.* (1999) *Curr. Biol.* 9:1177-1179.

Cenciarelli *et al.* teaches a polynucleotide comprising the sequence set forth as SEQ ID NO: 1 (see the attached sequence alignment), which meets the limitations of claims 9 and 10. Cenciarelli *et al.* further teaches a vector and host cell comprising said polynucleotide according to claims 6 and 11 (see especially Figure 2(a) and the caption thereto; the instant polynucleotide is referred to as "Fbw1a/β-Tcrp). Finally, the host cell of Cenciarelli *et al.* is a HeLa cell, which one of skill in the art would understand to be grown in a medium (i.e., tissue culture medium) that meets the limitations of "pharmaceutically acceptable carrier" as they are understood based on the discussion at paragraph 0130. Therefore, the composition comprising the host cell of Cenciarelli *et al.* anticipates the pharmaceutical composition of claim 13. As Cenciarelli *et al.*

teaches nucleic acids and host cells comprising all of the limitations of the instant claimed invention, Cenciarelli *et al.* anticipates the claims.

Claims 9 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by *Entrez* Nucleotide sequence, Accession No. AF061836 (gi:3126875), published 9 May 1998 (hereinafter, AF061836).

AF061836 discloses a nucleic acid comprising a sequence that is 98.2% identical to the instant SEQ ID NO: 3 over its full length. Thus, AF061836 anticipates the fragment of claim 9 and the variant of claim 10.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DMS

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